

APPENDIX 1

- 2 -

as an agent for improving lipid metabolism in hyperlipidemia patients (including familial hypercholesterolemia and xanthoma patients).

5 However, probucol also has a clinically
6 disadvantageous effect, i.e., reduces the cholesterol level
7 in the HDL fraction (hereinafter sometimes referred to as
8 "HDL-cholesterol"), unlike other lipid-lowering agents
9 which have the reaction properties in LDL such as statins
10 or fibrates (for example, refer to Non-Patent Documents 1
11 and 2). As the statin lipid-lowering agents, pravastatin
12 and simvastatin known as HMG-CoA reductase inhibitors are
13 known. As the fibrate lipid-lowering agents, fenofibrate
14 and bezafibrate are known. It is thought that this
15 reduction in HDL-cholesterol is due to functional
16 inhibition of ABCA1 (for example, refer to Non-Patent
17 Documents 3, 4, and 5).

18 It is known that probucol spiroquinone, probucol
19 diphenquinone, and probucol bisphenol according to the
20 present invention are produced as metabolites when probucol
21 is orally administered to a mammal (for example, prefer to
22 Non-Patent Document 6).

23 Some pharmacological activities of probucol
24 spiroquinone, probucol diphenquinone, and probucol
25 bisphenol (hereinafter sometimes preferred to as
26 "bisphenol-type compounds", or collectively the "bisphenol-
27 type compound") are known at present. For example, it is
28 disclosed that probucol bisphenol has antioxidant
29 properties and is used in combination with probucol as a
30 lipoprotein oxidation inhibitor (for example, refer to
31 Patent Document 1). In addition, it is known that the
32 bisphenol-type compounds incorporate cholesterol into cells
33 (for example, refer to Non-Patent Document 7). However, in
34 these prior findings, functions of the bisphenol-type
35 compounds on ABCA1 and HDL are not disclosed at all.

 HDL is a lipid/protein complex particle produced
by the action of helix-like apolipoproteins such as

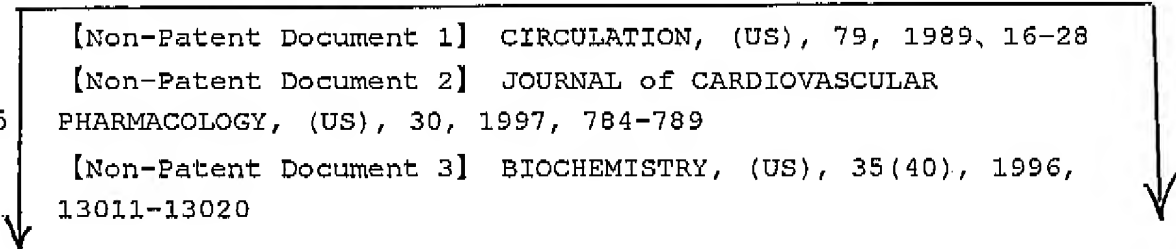
engineering technology.

For example, for increasing cholesterol efflux and HDL levels, the expression level and activity of ABCA1 are elevated by direct gene transfer of an ABCA1-coding
5 gene into a host cell (for example, refer to Patent Documents 2 and 3). The expression and activity of ABCA1 are increased by using a certain substance to facilitate the transcription and translation of the ABCA1 gene for controlling the levels of HDL cholesterol and triglyceride
10 (for example, refer to Patent Document 4). Furthermore, for controlling the cholesterol efflux to the outside of cells, the expression of ABCA1 is increased by activating peroxisome proliferator activated receptor- α (PPAR- α) or peroxisome proliferator activated receptor- δ (PPAR- δ) having
15 various activities as an intranuclear receptor (for example, refer to Patent Document 5).

However, in the above-mentioned known technologies focused on ABCA1 and HDL, a genetic engineering technology or a method for activating an
20 intranuclear receptor is used. Therefore, there are disadvantages such that the technology for a genetic therapy is immature and that a risk of unexpected side effects caused by activating an unknown gene is not ignorable. Thus, the use as a drug has not been
25 accomplished yet.

【Patent Document 1】 International Publication WO 02/04031
【Patent Document 2】 International Publication WO 00/78971
【Patent Document 3】 International Publication WO 00/78972
30 【Patent Document 4】 International Publication WO 01/15676
【Patent Document 5】 Japanese Unexamined Patent Application Publication No. 2003-12551

35 【Non-Patent Document 1】 CIRCULATION, (US), 79, 1989, 16-28
【Non-Patent Document 2】 JOURNAL of CARDIOVASCULAR PHARMACOLOGY, (US), 30, 1997, 784-789
【Non-Patent Document 3】 BIOCHEMISTRY, (US), 35(40), 1996, 13011-13020



↑ 【Non-Patent Document 4】 BIOCHIMICA et BIOPHYSICA ACTA,
(Netherlands), 1483, 2000, 199-213

 【Non-Patent Document 5】 Arteriosclerosis, thrombosis, and
 vascular biology, (US), 21, 2001, 394-400

5 【Non-Patent Document 6】 ANALYTICAL CHEMISTRY SYMPOSIA
SERIES, (US), 7, 1981, 35-38

 【Non-Patent Document 7】 LIPIDS, (US), 29(12), 1994, 819-
823

10 【Non-Patent Document 8】 ANNUAL REVIEW of CELL BIOLOGY,
(US), 8, 1992, 67-113

 【Non-Patent Document 9】 NATURE GENETICS, (US), 22, 1999,
336-345

 【Non-Patent Document 10】 NATURE GENETICS, (US), 22, 1999,
347-351

15 【Non-Patent Document 11】 NATURE GENETICS, (US), 22, 1999,
352-355

 【Non-Patent Document 12】 THE JOURNAL of CLINICAL
INVESTIGATION, (US), 104, 1999, R25-R31

20 【Non-Patent Document 13】 THE FASEB JOURNAL, (US), 15, 2001,
1555-1561

SUMMARY OF THE INVENTION

25 As described above, low-HDL cholesterolemia is
often observed in hyperlipidemia, obesity, and diabetes
mellitus and is a serious risk factor of arterioscleroses
such as myocardial infarction, cerebral infarction, and
cerebral apoplexy. The present invention provides a
30 prophylactic/therapeutic agent for various diseases such as
arteriosclerosis based on mechanisms wherein ABCA1 is
stabilized with a specific bisphenol-type compound, thereby
resulting in elevating ABCA1 levels followed by an increase
in production of HDL.

35

 The present inventors have studied for various
materials in order to overcome the above-mentioned

APPENDIX 2

List of Non-Patent Documents quoted in the Specification

Non-Patent Document		Outline
1	Circulation, 79, p16-28, 1989	p16 [Abstract] ...whereas probucol decreased HDL 29%. p20 [FIGURE.4] and p21, right column, line 6 from the bottom ...probucol therapy alone produced a 29% decrease in HDL cholesterol levels.
2	J. Cardiovascular pharmacology, 30, p784-789, 1997	p784 [Abstract] ...Most of the patient (90%) also responded with a reduction of high-density lipoprotein cholesterol (HDL-C);...
3	Biochemistry, 35(40), p13011-13020, 1996	P13011 [Abstract] ...apparent cellular cholesterol efflux to high-density lipoprotein (HDL) was reduced by probucol by 40-70% while the rate of cholesterol influx from HDL to the cells was unaffected, resulting in cancellation of the net cellular cholesterol efflux to HDL,...
4	Biochimica et Biophysica Acta, 1485, p199-213, 2000	p199 [Abstract] ...the mRNA levels of the potential regulatory proteins of the HDL level such as apoA-I, apoE, LCAT, PLTP, SRB1, and ABC1 did not change with probucol... p209, left column, line 15 from the bottom The reduction of plasma HDL should therefore be attributed to the inhibition by probucol of the apocell interaction in vivo.
5	Arteriosclerosis, thrombosis, and vascular biology, 21, p394-400, 2001	p397, left column, line 1 from the bottom ...Probucol, which reduces plasma HDL, has been shown to interfere with the cellapolipoprotein interaction to inhibit the generation of HDL in vitro and in vitro and to induce tissue cholesterol accumulation in a certain strain of mouse....

APPENDIX 3

Shinji YOKOYAMA et al.
Serial No. 10/586,338
Attorney Docket No. 2006_1127A
May 18, 2009

probucol bisphenol inherently stabilizes ABCA1.

Applicants' Arguments

As discussed above, Applicants' amended claims recite a method for increasing expression of ABCA1.

Stocker discloses that probucol and probucol-derived bisphenol exert anti-oxidation. For diphenoquinone, Stocker discloses:

The corresponding oxidation product, diphenoquinone, is incapable of acting as an co-antioxidant, as judged by its high anti-TMP index and inability to cause the decay of α -tocopheroxyl radical (Table 8).

(Please see page 26, lines 13 to 16 of Stocker, attached hereto as Appendix 2.)

Additionally, probucol spiroquinone (SQ) has no anti-oxidation activity. This fact is verified through experiments. Please see Figure 4A of the unpublished document, Arakawa et al., "Pharmacological Inhibition of ABCA1 Biodegradation Increases HDL Biogenesis and Exhibits Antiatherogenesis", attached hereto as Appendix 3.

In addition, as apparent from the presumable metabolism pathway of probucol (Appendix 4), probucol diphenoquinone (DQ) is an SQ-derived metabolite product, derived by oxidation of SQ. Therefore, one of ordinary skill in the art must readily infer that the oxidation activity of DQ is weaker than that of SQ.

The Stocker document is based on the concept that an inhibitor of lipoprotein oxidation would be assumed to be useful in treatment of atherosclerosis. Stocker never teaches or suggests increasing expression of ABCA1 with a bisphenol compound selected from the group consisting of probucol spiroquinone (SQ), probucol diphenoquinone (DQ) and probucol bisphenol (BH).

The Examiner states, "it is assumed that the probucol inherently stabilizes ABCA1." However, this assumption is moot because neither probucol spiroquinone (SQ) nor probucol diphenoquinone (DQ) exert anti-oxidation activity, while probucol bisphenol (BH) is considered to be a co-antioxidant. If Examiner's assumption were correct, SQ and DQ would act as anti-oxidants or co-antioxidants in the same manner as BH.

The present invention is based on the novel discovery that probucol spiroquinone (SQ), probucol diphenquinone (DQ) and probucol bisphenol (BH) are effective stabilizers for ABCA1, which is a key molecule for controlling the level of blood HDL enabling lipids like cholesterol and triglycerides to be transported within the water-based blood stream.

As shown in Assay Example 1 of Applicants' specification, probucol spiroquinone (SQ), probucol diphenquinone (DQ) and probucol bisphenol (BH) all increase ABCA1 expression compared to the control. The cited reference fails to teach or suggest Applicants' claimed method.

Accordingly, it is respectfully requested that the above-rejection be withdrawn.

The rejection of claims 1-3 and 5 under 35 U.S.C. § 102(b) as being anticipated by McLean et al. (Lipids) has been rendered moot by the cancellation of the rejected claims. Applicants provide the following comments regarding the patentability of new claims 6 and 7 over the cited reference.

The Position of the Examiner

The Examiner takes the position that McLean et al. teach probucol, probucol spiroquinone (SQ), probucol diphenquinone (DQ) and probucol bisphenol (BH). The Examiner indicates that although McLean et al. do not teach that these compounds are ABCA1 stabilizers, their ability to stabilize ABCA1 would be inherent.

Applicants' Arguments

Again, Applicants note that the amended claims are directed to a method for increasing expression of ABCA1. McLean et al. merely disclose biological actions exerted by three probucol metabolites, probucol spiroquinone (SQ), probucol diphenquinone (DQ) and probucol bisphenol (BH), wherein said biological actions are only related to interactions with cholesterol esters and cholesterol incorporations (inclusions) into cells.

Particularly, for probucol spiroquinone (SQ) and probucol diphenquinone (DQ), it is noted that McLean et al. disclose the following: